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1 Bleeding changes after levonorgestrel 52mg intrauterine system insertion for
2 contraception in women with self-reported heavy menstrual bleeding

3

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21 BAC serves on an Advisory Board for Merck & Co. Magee-Womens Research

22 Institute has received funding for contraceptive research from Medicines360,

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24DLE serves on scientific advisory boards for FemaSys and Medicines360, is a
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55 **CONDENSATION**

56 Most women with self-reported heavy menstrual bleeding will have a rapid
57 decrease in flow following levonorgestrel 52mg intrauterine system
58 placement.

59

60 **SHORT TITLE**

61 LNG 52mg IUS treatment of HMB

62

63 **AJOG AT A GLANCE**

64 Why was the study conducted?

- 65 • To evaluate cycle-by-cycle decrease in self-reported heavy menstrual
66 bleeding (HMB) among women initiating levonorgestrel 52mg
67 intrauterine system (IUS) use.

68 What are the key findings?

- 69 • HMB decreases significantly even with the first period after insertion,
70 more than 90% of women no longer have subjective heavy bleeding
71 within 6 months, and amenorrhea rates during the first year are lower
72 than in women without self-reported baseline HMB.

73 What does this study add to what is already known?

- 74 • This study provides a cycle-by-cycle evaluation of bleeding changes,
75 showing how rapidly flow decreases after LNG 52mg IUS insertion in
76 U.S. women with self-reported HMB.

77

78 **ABSTRACT**

79 **Background:** The levonorgestrel 52mg intrauterine system (IUS) has proven
80 efficacy for heavy menstrual bleeding (HMB) treatment in clinical trials, but
81 little data exists to demonstrate how rapidly the effects occur and the effects
82 in women with self-reported heavy bleeding as seen commonly in clinical
83 practice.

84 **Objective:** Evaluate changes in bleeding patterns in women with self-
85 reported HMB prior to levonorgestrel 52mg IUS insertion.

86 **Study Design:** A total of 1,714 women aged 16-45 years old received a
87 levonorgestrel 52mg IUS in a multicenter trial evaluating contraceptive
88 efficacy and safety for up to 10 years. At screening, participants described
89 their baseline menstrual bleeding patterns for the prior 3 months.
90 Participants completed daily diaries with subjective evaluation of bleeding
91 information for the first 2 years. For this analysis, we included women with at
92 least one complete 28-day cycle of IUS use and excluded women using a
93 hormonal or copper intrauterine contraception in the month prior to study
94 enrollment. We evaluated changes in menstrual bleeding and discontinuation
95 for bleeding complaints per 28-day cycle over 26 cycles (2 years) in women
96 who self-reported their baseline pattern as heavy. We also compared rates of
97 amenorrhea, defined as no bleeding or spotting, within the entire study
98 population in women with subjective HMB at baseline compared to those who
99 did not complain of HMB.

Results: Of the 1513 women in this analysis, 150 (9.9%) reported baseline HMB. The majority of women reported no longer experiencing HMB by the end of cycle 1 (112/150, 74.7%) with even higher rates by cycle 2, (124/148, 83.8%). At the end of cycles 6, 13 and 26, 129/140 (92.1%, 95% CI 87.7-96.6%), 114/123 (92.7%, 95% CI 88.1-97.3%) and 100/103 (97.1%, 95% CI 93.8-100%) women reported no HMB, respectively. After cycles 13 and 26, 63/123 (51.2%, 95% CI 42.4-60.1%) and 66/103 (64.1%, 95% CI 54.8-73.3%), respectively, reported their bleeding as amenorrhea or spotting only. A lower proportion of women with baseline self-reported HMB reported amenorrhea as compared to women in the overall study cohort without HMB at the end of 6 cycles (319 [25.5%] vs. 21 [15.0%], $p=.005$) and 13 cycles (382 [34.4%] vs. 26 [21.1%], $p=.003$); differences were not significant after 19 cycles (367 [37.2%] vs. 36 [31.0%], $p=.022$) and 26 cycles (383 [43.5%] vs. 38 [36.9%], $p=.21$). Only 4 (2.7%) women with baseline HMB discontinued for bleeding complaints (2 for HMB and 2 for irregular bleeding), all within the first year.

Conclusions: Most women who self-report HMB experience significant improvement quickly after levonorgestrel 52mg IUS insertion. Discontinuation for bleeding complaints among women with baseline HMB is very low.

119

120 **KEY WORDS**

121 Heavy menstrual bleeding, menorrhagia, Intrauterine device, Intrauterine
122 system, Liletta, Amenorrhea

123Introduction

124 Normal menstrual blood loss (MBL) ranges between 20 and 60
125mL/cycle. Heavy menstrual bleeding (HMB), formerly referred to as
126menorrhagia, is excessive blood loss that occurs alone or in combination with
127other symptoms and has a negative impact on a woman's physical, social,
128emotional, and material quality of life (1). Although studies for agency
129approval typically define HMB as $MBL \geq 80$ mL per cycle, only about half of
130women who complain of HMB meet these criteria (1,2).

131 Approximately 30% of women are affected by HMB during their
132reproductive years, resulting in increased health costs (3). A variety of
133functional, structural, and non-structural conditions can cause HMB, including
134adenomyosis, leiomyomas, and coagulopathies as well as iatrogenic causes.
135In many women, the underlying cause of HMB is unknown and is referred to
136as functional HMB (4).

137 In the early 1990s, the levonorgestrel 52mg intrauterine system (IUS)
138emerged as an option for medical management of HMB. While oral
139progestins have variable effects, combined oral contraceptives, non-steroidal
140anti-inflammatory drugs and antifibrinolytics can reduce MBL by 40-50%
141within a few cycles of treatment, a levonorgestrel 52mg IUS can decrease
142measured MBL by 71% within 6 months and up to 94% after 1 year (5,6).
143Additionally, the levonorgestrel 52mg IUS provides greater improvement in
144women's assessment of the effect of HMB on their daily routine and

145psychological and physical well-being compared to usual medical treatment
146(1,7-9).

147 Although data from clinical trials evaluate outcomes in women with a
148quantifiable level of blood loss per cycle, clinical guidelines recognize that
149the diagnosis should be based on subjective measures rather than the
150objective measure of MBL because HMB has a major impact on a woman's
151quality of life, (10). No prospective study has reported the impact of a
152levonorgestrel 52mg IUS in U.S. women with "real-life" HMB. This report
153describes bleeding changes and outcomes over the first two years of
154levonorgestrel 52mg IUS use among participants in a Phase 3 contraceptive
155trial who self-reported baseline HMB.

156

157**Materials and Methods**

158 This secondary analysis includes data from the ACCESS IUS (A
159Comprehensive Contraceptive Efficacy and Safety Study of an IUS)
160multicenter, open-label trial of Liletta® (Medicines360, San Francisco, CA and
161Allergan, Irvine, CA; Liletta® is a registered trademark of Odyssea Pharma
162SPRL [Belgium], an Allergan affiliate). The methods of the primary study
163have been reported previously (11). Briefly, investigators at 29 sites in the
164United States enrolled healthy nulliparous and parous women aged 16-45
165years (inclusive) who desired a hormonal intrauterine system (IUS) for
166contraception from December 2009 to April 2013. Entry criteria included
167regular menstrual cycles every 21-35 days with a typical cycle length

168variation of no more than five days and no abnormality of the uterus
169resulting in distortion of the cavity incompatible with insertion. A local or
170central Institutional Review Board approved the study for each site. Each
171woman signed written informed consent before study participation.

172 At screening, investigators asked participants to describe their
173baseline and worst menstrual bleeding patterns for the prior 3 months as
174light, normal or heavy flow. We defined self-reported HMB as a response of
175heavy flow for both questions. Follow-up during the first year included visits
176at one, three, six and 12 months, and a telephone contact at month nine.
177Participants completed a daily paper diary to indicate the greatest amount of
178bleeding that day as none, spotting, light flow, normal flow, or heavy flow
179based on their subjective impression. Details of diary instructions and
180completion have been previously published (12). We only included qualifying
181cycles for bleeding-related calculations, defined as 23 or more days of
182reporting, and did not impute any missing data.

183 All analyses only included women who had successful IUS insertion,
184were not using any intrauterine contraception in the month prior to insertion,
185attended at least one follow-up visit, and had at least one qualifying cycle of
186diary data. We compared demographic characteristics, bleeding patterns
187and discontinuation rates among women with and without self-reported HMB
188at baseline. We evaluated bleeding patterns and discontinuation rates in 28-
189day intervals (“cycles”) and defined amenorrhea as no bleeding or spotting
190during the cycle. We used Fisher’s exact test for comparisons of proportions.

191 We used SAS® 9.3 (Cary, NC) with a p-value of .05 considered statistically
192 significant.

193

194 **Results**

195 Of the 1714 women who enrolled and had successful placement, 1691
196 women completed at least one 28-day cycle of follow-up. We excluded 178
197 women who had been using intrauterine contraception in the month prior to
198 enrollment. Of the 1513 women in the analysis population, 150 (9.9%) self-
199 reported HMB during the 3 months prior to enrollment. We present
200 participant characteristics in Table 1; of note, women with baseline HMB
201 were more likely to be African-American.

202 Changes in bleeding patterns are presented in Figure 1. By the 28th
203 day of levonorgestrel 52mg IUS use, 112 (74.7%, 95% CI 67.7-81.6%) women
204 reported the absence of subjectively heavy bleeding. By the end of cycle 2,
205 124 (83.8%, 95% CI 77.8-89.7%) of the 148 women that started the cycle
206 reported no HMB. At the end of cycles 6, 13 and 26, 129/140 (92.1%, 95% CI
207 87.7-96.6%), 114/123 (92.7%, 95% CI 88.1-97.3%) and 100/103 (97.1%, 95%
208 CI 93.8-100%) women reported no HMB, respectively. After cycles 13 and 26,
209 63/123 (51.2%, 95% CI 42.4-60.1%) and 66/103 (64.1%, 95% CI 54.8-73.3%),
210 respectively, reported their bleeding as amenorrhea or spotting only.
211 Amenorrhea rates are reported in Table 2. Of note, women who self-report
212 baseline HMB had significantly lower amenorrhea rates than the remainder

213of the levonorgestrel 52mg IUS user population, but only during the first 13
214cycles of IUS use.

215 Women with baseline HMB did not discontinue IUS use more or less
216frequently than those women who did not report subjective baseline HMB
217(Table 3). Only 4 (2.7%) women with baseline HMB discontinued for bleeding
218complaints (2 for HMB and 2 for irregular bleeding), all within the first year.
219These rates did not differ from the discontinuation rates for bleeding
220complaints in the remainder of the study population (Table 3). The reasons
221for discontinuation did not differ between women with and without subjective
222baseline HMB (Table 4).

223

224**Comment**

225Principal Findings

226 We found that women with self-reported HMB have a very rapid and
227dramatic decrease in flow following levonorgestrel 52mg IUS insertion.
228Three-fourths of women report no HMB after just one cycle. During the first
229year of use, women with self-reported HMB report significantly lower
230amenorrhea rates compared to women not reporting HMB. Amenorrhea rates
231in the 6th and 13th cycle of levonorgestrel 52 mg IUS use are 60-70% higher
232in women without subjective HMB (Table 2).

233Results

234 These findings represent women's subjective views of their bleeding
235patterns, which differ from studies in which women are enrolled to test a

236treatment for HMB for regulatory approval. These HMB treatment studies
237require blood loss quantification to ensure a baseline MBL ≥ 80 mL per cycle.
238Although the studies for regulatory approval measure changes in blood loss,
239they do not describe how quickly blood flow decreases in each of the first
240few months, as was shown in our current study. The two available
241levonorgestrel 52mg IUS products are approved in various countries
242throughout the world as a treatment for HMB based on such studies (4,7). A
243multicenter, single-blind randomized trial in Eastern Europe compared the
244two available levonorgestrel 52mg IUS products in patients with HMB
245utilizing a pictorial blood loss chart to assess MBL and demonstrated equal
246decreases in MBL and increases in ferritin and hemoglobin (4), resulting in
247European Medicines Agency approval of Levosert® (Liletta) in Europe. In the
248U.S., only Mirena® (Bayer Healthcare, Whippany, NJ) is currently approved
249for HMB treatment in women desiring an IUS for contraception. In the trial for
250Food and Drug Administration approval, 642 of 807 (79.6%) women failed
251screening, typically because of blood loss that did not meet the 80 mL per
252cycle criterion (7). Thus, it is possible that most women with self-reported
253HMB do not have the degree of MBL evaluated in studies for regulatory
254approval. Although many women who self-report HMB in the general
255population may not have MBL ≥ 80 mL per cycle, these women still recognize
256subjectively significant bleeding reduction.

257 Whereas first-line treatment for HMB includes the levonorgestrel 52mg
258IUS (13,14), currently available lower dose levonorgestrel IUS products have

259not demonstrated efficacy for HMB treatment. When flow patterns are
260evaluated in young women using a levonorgestrel IUS, more women using
261lower dose products experience prolonged or heavy flow as compared to a
26252mg product (15).

263Clinical Implications

264 This information is important for counseling women with self-reported
265HMB about the expected outcome when using the levonorgestrel 52mg IUS
266for therapeutic purposes to decrease subjectively heavy menstrual flow.
267Although much has been published about the decrease in menstrual flow in
268women using a levonorgestrel 52mg IUS for HMB (16), little is known about
269the effects in women with HMB using the product primarily for contraception.
270Because HMB significantly increases with age (17), women who use a LNG
271IUS primarily for HMB likely differ in age and other characteristics from those
272who use it primarily for contraception. Studies evaluating HMB treatment
273with the levonorgestrel 52mg IUS for agency approval in the United States
274and Europe had an average age of 38 years (4,7) whereas women in the
275ACCESS IUS contraceptive trial with self-reported HMB had an average age of
27627.5 years.

277Strengths and Limitations

278 A strength of this study is the findings in a diverse population of
279women and daily collection of flow in a diary. Even with this diversity, we are
280not powered to adequately evaluate potential racial differences in
281amenorrhea rates or rare outcomes such as discontinuation for bleeding

282 concerns among women with self-reported baseline HMB. A weakness is that
283 the outcomes represent the strictest definitions of bleeding; for example,
284 one day of spotting would count as non-amenorrheic. Accordingly, to
285 understand the true decrease in bleeding, the rates of amenorrhea or
286 spotting rather than amenorrhea alone provide more realistic information for
287 counseling patients. At one year and beyond, approximately 50%-60% of
288 women will report amenorrhea or spotting, with about two-thirds of this
289 pattern as spotting.

290 Research Implications

291 The number of women in racial subgroups when evaluating
292 amenorrhea and discontinuation due to bleeding complaints is too low to
293 discriminate these outcomes, especially the rare outcome of discontinuation
294 for a bleeding complaint in women with self-reported HMB. Very large
295 population-based studies could address these issues.

296 Conclusions

297 These findings demonstrate the expected outcomes within young
298 women with self-reported heavy bleeding using the levonorgestrel 52mg IUS
299 for contraception. A potential benefit of levonorgestrel 52mg IUS use by
300 women choosing this method for contraception is the significant decrease in
301 flow. Clinicians can use the information provided in this report to better
302 counsel women based on their baseline subjective bleeding pattern.

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357 bleeding. Cochrane Database Syst Rev 2015;4:CD002126.
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360Table 1. Demographics at enrollment for women with and without pre-study
361self-reported HMB* in a phase 3 study of a levonorgestrel 52mg IUS
362(N=1513)

Characteristic	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value
Age (years)	27.5 ± 5.8	26.8 ± 5.5	.17
≥36	13 (8.7%)	96 (7.0%)	.50
Ethnicity			.22
Hispanic or Latina	26 (17.3%)	186 (13.6%)	
Race			.007
White	99 (66.0%)	1079 (79.2%)	
Black or African American	36 (24.0%)	168 (12.3%)	
Asian	8 (5.3%)	55 (4.0%)	
Multiracial	4 (2.7%)	36 (2.6%)	
American Indian or Alaska Native	3 (2.0%)	16 (1.2%)	
Native Hawaiian or Other Pacific Islander	0	5 (0.4%)	
Data missing	0	4 (0.3%)	
Body Mass Index (kg/m²)	28.6 ± 7.2	26.7 ± 6.6	.001
Obese (≥30.0)	47 (31.3%)	328 (24.1%)	.06
Parity			
Nulliparous	84 (56.0%)	839 (61.6%)	.19
Marital Status			.58
Never married	93 (62.0%)	896 (65.7%)	
Married	41 (27.3%)	358 (26.3%)	
Divorced	14 (9.3%)	85 (6.2%)	
Separated	2 (1.3%)	22 (1.6%)	
Widowed	0	2 (0.1%)	

363

364* based on self-report of menstrual bleeding patterns for the 3 months prior
365to screening

366Data are presented as n (%) or mean \pm standard deviation
367HMB=heavy menstrual bleeding; IUS=intrauterine system

368Table 2. Amenorrhea rates over 2 years (26 cycles) of levonorgestrel 52mg IUS use among women with
369and without self-reported baseline HMB* (N=1513)

370

Cycles of use	Women with baseline HMB n=150		Women without baseline HMB n=1363		p-value [†]
	Number entering cycle	Amenorrhea rate	Number entering cycle	Amenorrhea rate	
6	140	21 (15.0%, 9.1-20.9%)	1251	319 (25.5%, 23.1- 27.9%)	.005
13	123	26 (21.1%, 13.9- 28.4%)	1112	382 (34.4%, 31.6- 37.1%)	.003
19	116	36 (31.0%, 22.6- 39.5%)	987	367 (37.2%, 34.2- 40.2%)	.22
26	103	38 (36.9%, 27.6- 46.2%)	880	383 (43.5%, 40.2- 46.8%)	.21

371

372Data are presented as n (% , 95% confidence interval).

373HMB=heavy menstrual bleeding; IUS = intrauterine system

374* based on self-report of menstrual bleeding patterns for the 3 months prior to screening

375[†] Fisher exact test

376

377Table 3. Cumulative discontinuation rates over 2 years (26 cycles) of levonorgestrel 52mg IUS use among
378women with and without self-reported baseline HMB* (N=1513)

379

Cycle s of use	Discontinuation overall			Discontinuation for bleeding complaint		
	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value [†]	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value [†]
3	5 (3.3%, 0.5-6.2%)	50 (3.7%, 2.7-4.7%)	1.0	0	2 (0.1%, 0.0-0.3%)	1.0
6	9 (6.0%, 2.2-9.8%)	108 (7.9%, 6.5-9.4%)	.52	0	6 (0.4%, 0.1-0.8%)	1.0
9	17 (11.3%, 6.3-16.4%)	163 (12.0%, 10.2-13.7%)	.89	1 (0.7%, 0.0-2.0%)	8 (0.6%, 0.2-1.0%)	.61
13	26 (17.3%, 11.3-23.4%)	246 (18.0%, 16.0-20.1%)	.91	3 (2.0%, 0.0-4.2%)	13 (1.0%, 0.4-1.5%)	.21
19	32 (21.3%, 14.8-27.9%)	364 (26.7%, 24.4-29.1%)	.17	4 (2.7%, 0.1-5.2%)	22 (1.6%, 0.9-2.3%)	.32
26	42 (28.0%, 20.8-35.2%)	454 (33.3%, 30.8-35.8%)	.20	4 (2.7%, 0.1-5.2%)	26 (1.9%, 1.2-2.6%)	.53

380

381Data are presented as n (% , 95% confidence interval).

382HMB=heavy menstrual bleeding; IUS = intrauterine system

383* based on self-report of menstrual bleeding patterns for the 3 months prior to screening

384[†] Fisher exact test

385

386Table 4. Reasons for discontinuation over 2 years (26 cycles) of levonorgestrel 52mg IUS use among
 387women with and without self-reported baseline HMB* (N=1513)

388

Reason for discontinuation	Women with baseline HMB n=150	Women without baseline HMB n=1363	p-value [†]
Adverse event (not including expulsion or bleeding complaint)	12 (5.3%)	136 (8.1%)	.56
Lost to follow-up/withdrew consent	8 (5.3%)	126 (9.2%)	.13
Expulsion	7 (4.7%)	39 (2.9%)	.21
Desires pregnancy	5 (3.3%)	43 (3.2%)	.81
Bleeding complaint	4 (2.7%)	26 (1.9%)	.53
Subject relocation	3 (2.0%)	28 (2.8%)	1.0
Other	3 (2.0%)	56 (4.1%)	.27

389

390Data are presented as n (%).

391HMB=heavy menstrual bleeding; IUS = intrauterine system

392* based on self-report of menstrual bleeding patterns for the 3 months prior to screening

393[†] Fisher exact test

Figure Legend

Figure 1.

Title:

Flow patterns after levonorgestrel 52mg IUS insertion in women with self-reported baseline HMB*

Footer:

* Number of women with HMB at baseline is 150; proportion for each cycle is calculated based on the number of women using the levonorgestrel 52mg IUS during that cycle.

HMB=heavy menstrual bleeding; IUS=intrauterine system

